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Abbreviations

BUN, blood urea nitrogen; BMI, body mass index; CV, coefficient of variation; DMSA, dimercaptosuccinic acid; EDTA, calcium disodium ethylenediamine tetraacetic acid; NAG, N-acetyl-β-D-glucosaminidase; NO, nitric oxide; RBP, retinol-binding protein; SD, standard deviation

ABSTRACT

Recent research suggests that both uric acid and lead may be nephrotoxic at lower levels than previously recognized. Data from 803 current and former lead workers were analyzed to determine whether lead biomarkers were associated with uric acid and whether previously reported associations between lead dose and renal outcomes were altered after adjustment for uric acid. Outcomes included uric acid, blood urea nitrogen, serum creatinine, measured and calculated creatinine clearances, and urinary N-acetyl-β-D-glucosaminidase (NAG) and retinol-binding protein. Mean (SD) uric acid, tibia lead, and blood lead levels were 4.8 (1.2) mg/dl, 37.2 (40.4) μg/g bone mineral, and 32.0 (15.0) μg/dl, respectively. None of the lead measures (tibia, blood, and dimercaptosuccinic acid chelatable lead) was associated with uric acid, after adjustment for age, gender, body mass index, and alcohol use. However, when effect modification by age on these relations was examined, both blood and tibia lead were significantly associated ($\beta = 0.0111$; $p < 0.01$ and $\beta = 0.0036$; $p = 0.04$, respectively) in participants in the oldest age tertile. These associations decreased after adjustment for blood pressure and renal function, although blood lead remained significantly associated with uric acid ($\beta = 0.0156$; $p = 0.01$) when the population was restricted to the oldest tertile of workers with serum creatinine greater than the median (0.86 mg/dl). Next, in models of renal function in all workers, uric acid was significantly ($p < 0.05$) associated with all renal outcomes except NAG. Finally, in the oldest tertile of workers, associations between lead dose and NAG were unchanged, but fewer associations between the lead biomarkers and the clinical renal outcomes remained significant ($p \leq 0.05$) following adjustment for uric acid. In conclusion, our data suggest that older workers comprise a susceptible population for increased uric acid due to lead. Uric acid may be one, but not the only, mechanism for lead-related nephrotoxicity.

INTRODUCTION

Historically, gout was common among patients with lead poisoning (Batuman 1993). More recently, associations between various measures of lead dose and serum uric acid (urate) levels have been reported in studies of occupationally exposed populations (Ehrlich et al. 1998; Wang et al. 2002) as well as in general population studies (Lin et al. 2002; Shadick et al. 2000). These associations are present at much lower lead doses than those associated with gout in historical lead poisoning. Lead exposure also increases the risk for adverse renal outcomes. Lead has been reported to cause nephrotoxicity by several mechanisms, although it is not known which of these is the predominant pathway (Nolan and Shaikh 1992; Sanchez-Fructuoso et al. 2002; Vaziri 2002). Uric acid is also a nephrotoxicant, and increasing evidence suggests that this toxicity occurs at lower levels than previously recognized (Johnson et al. 2003). Several adverse renal and vascular outcomes have been reported in a recently developed rodent model of low level hyperuricemia, including hypertension and tubulointerstitial fibrosis (Mazzali et al. 2001a), renal afferent arteriolopathy (Mazzali et al. 2002), glomerular hypertrophy, glomerulosclerosis (Nakagawa et al. 2003), and glomerular hypertension (Sanchez-Lozada et al. 2002). More importantly, uric acid in this model accelerates renal dysfunction from other causes (Kang et al. 2002; Mazzali et al. 2001b). This raises the intriguing possibility that increased uric acid is one mechanism by which lead causes nephrotoxicity.

In our recently reported analyses of data from the first of three evaluations in a longitudinal study of the health effects of inorganic lead exposure in 803 current and former lead workers (Weaver et al. 2003), we found associations between lead exposure and dose measures and adverse renal function outcomes. Lead measures were associated with decreased renal function, primarily in the oldest tertile of workers (> 46 years old). Therefore, we analyzed data from the entire population of lead workers and conducted separate analyses of the oldest tertile of workers in some models, to determine whether the lead biomarkers were associated with uric

acid, and whether uric acid levels were associated with renal function outcomes. In addition, we evaluated whether relations between the lead biomarkers and renal outcomes were altered after adjustment for uric acid.

MATERIALS AND METHODS

Study overview and design

Data from 803 current and former lead workers who completed the first of three annual evaluations in a longitudinal study of the renal, vascular, hematopoietic, and nervous system effects of inorganic lead exposure are reported. Participants were evaluated between October 24, 1997 and August 19, 1999. All participants provided written, informed consent. The study protocol was approved by Institutional Review Boards at the SoonChunHyang University and the Johns Hopkins University Bloomberg School of Public Health. Participation in the study was voluntary, and workers were paid approximately $30 for their time and effort.

Study population

As previously described (Schwartz et al. 2001; Weaver et al. 2003), workers were recruited from 26 different plants that produced lead batteries, lead oxide, lead crystal, or radiators, or were secondary lead smelters. Workers were designated as lead workers based on the potential for exposure to lead in the manufacturing process. No medical exclusionary criteria were used. Study participants were not currently occupationally exposed to other known renal toxicants.

Data collection

Data collection was completed either at the Institute of Industrial Medicine of the SoonChunHyang University in Chonan or at the study plants, using previously reported methods (Schwartz et al. 2001; Weaver et al. 2003). Data and biological specimens collected included: a standardized questionnaire on demographics, medical history, and occupational history; blood pressure measured with a Hawksley random zero sphygmomanometer (Lee B-K et al. 2001); height and weight measurement; a blood specimen (for blood lead, blood urea nitrogen [BUN], serum creatinine, and uric acid); a spot urine sample (for N-acetyl-β-D-glucosaminidase [NAG]; retinol-binding protein [RBP] and creatinine); and tibia lead concentration. A four-hour urine

collection after oral administration of 10 mg/kg DMSA was also obtained to measure DMSA-chelatable lead and creatinine clearance (787 participants completed this collection).

Laboratory methods

The lead biomarkers and renal outcomes were measured using previously reported assays (Schwartz et al. 2001; Weaver et al. 2003). In brief, blood lead was measured (Fernandez 1975) with an Hitachi 8100 Zeeman background-corrected atomic absorption spectrophotometer (Hitachi Ltd. Instruments, Tokyo, Japan) at the Institute of Industrial Medicine, a certified reference laboratory for lead in South Korea. Tibia lead was assessed via a 30-minute measurement of the left mid-tibia diaphysis using ^{109}Cd in a back-scatter geometry to fluoresce the K-shell X-rays of lead. The lead X-rays are recorded with a radiation detector and are then quantified and compared to calibration data to estimate the concentration of lead in bone (Todd and Chettle 1994; Todd and McNeill 1993). The emitted K-shell X-rays are attenuated as they pass through bone and overlying tissues. The lead X-rays are therefore normalized to the amount of elastic scattering from the bone itself to yield a measurement accuracy that is independent of the distance between the radiation source and the subject, subject positioning, small subject movements, overlying tissue thickness, and bone size, shape, geometry and density (Todd 2000a, 2000b; Todd and Chettle 1994; Todd and McNeill 1993). All point estimates, including negative values, were retained in the statistical analyses, in order to minimize bias and to avoid censoring of data (Kim et al. 1995). Urine lead levels in the four hour collection were measured at the Wadsworth Center of the New York State Department of Health (Albany, NY, USA) by electrothermal atomic absorption spectrometry with Zeeman background correction (Perkin-Elmer Model 4100ZL, Norwalk, CT, USA) (Parsons and Slavin 1999). BUN, serum creatinine, and uric acid were measured via an automatic chemical analyzer (Toshiba TBA 40FR Biochemical Analyzer, Tokyo, Japan). Urine creatinine was measured in spot samples (for adjustment of NAG and RBP) and in the four hour sample after DMSA (for determination of

measured creatinine clearance and adjustment of DMSA-chelatable lead levels), using a modification of the Sigma kit (St. Louis, MO, USA) assay (Weaver et al. 2000). Measured creatinine clearance was defined as: ([urinary creatinine in mg/dl x urine volume in ml] / serum creatinine in mg/dl) / collection time in minutes. Calculated creatinine clearance was obtained from the Cockcroft-Gault equation (Cockcroft and Gault 1976). NAG activity (expressed in μmol substrate converted per hour) was measured using the P.P.R. NAG test kit (P.P.R. Diagnostics, Ltd.; London, UK) and RBP was measured using a modification of the method of Topping and co-workers (Topping et al. 1986). As previously reported in Weaver et al. (2003), mean between-day coefficient of variation (CV) for 138 random NAG samples assayed in duplicate was 6.0 %; the CV for RBP was 7.4% (75 samples assayed in duplicate).

Statistical analysis

The overall goal of the analysis was to develop models that would allow hypotheses to be generated regarding causal pathways involving lead, uric acid, blood pressure, and renal function. As shown in Figure 1, these variables are biologically inter-related. As a result, adjustment for co-variates presents unique challenges. Adjustment for renal function and blood pressure likely results in over-control when associations between lead measures and uric acid are being evaluated. This is due to the fact that renal dysfunction and elevated blood pressure are risk factors for increased uric acid (Wortmann and Kelley 2001) and both can be caused or exacerbated by lead dose; thus they may be in the causal pathway between lead and uric acid. On the other hand, since non-lead related factors contribute to both renal dysfunction and elevated blood pressure, lack of adjustment for these variables in such models likely results in residual confounding. The inter-relatedness of these variables, as it relates to the potential for confounding versus causality, has been extensively discussed in the literature pertaining to uric acid as a risk factor for adverse cardiac, vascular, and renal outcomes (Johnson et al. 2003). Therefore, we have presented our data both with and without additional adjustment.

Analysis in these current and former lead workers was directed toward the following steps: 1) to evaluate associations of three lead dose biomarkers (tibia lead, blood lead, and DMSA-chelatable lead) with uric acid, with and without control for blood pressure and renal function, while controlling for other covariates (Figure 2A); 2) to evaluate associations between uric acid and six renal function outcomes (BUN, serum creatinine, measured creatinine clearance, calculated creatinine clearance, RBP, and NAG), with and without control for lead, while adjusting for blood pressure and other covariates (Figure 2B); and 3) to determine whether relations among these lead biomarkers and the six renal outcomes were altered by adjustment for uric acid, while controlling for other covariates, including blood pressure (Figures 2C). Statistical analysis was completed using software programs of the SAS Institute, Inc. (Cary, NC, USA).

Initially, variable distributions were examined. The distributions of NAG and RBP showed departures from normality and were thus ln-transformed; the adequacy of this transformation was subsequently confirmed by examination of the residuals from regression models. Linear regression modeling was used to evaluate associations between lead measures and both uric acid and renal function as outcomes, in separate models. Covariate selection for regression models of uric acid as the outcome utilized *a priori* variables (age, gender, and body mass index [BMI; weight in kilograms divided by the square of height in meters]) in modeling that initially included other biologically relevant variables in separate models. Variables with p-values < 0.1 were then modeled together and those with significant p-values in the combined model were retained. The additional covariates assessed included diabetes and hypertension (both based on participant report of physician diagnosis), use of analgesics (based on questionnaire data on medication usage), work status (current vs. former lead worker), systolic and diastolic blood pressure, renal function (BUN, serum creatinine, measured creatinine clearance, and calculated creatinine clearance), tobacco use, and alcohol consumption. Serum

creatinine was selected as the measure of renal function in the uric acid models, since the proportion of variance explained by the model when it was included ($r^2 = 0.37$) was the highest, compared to the other renal outcome measures. Continuous independent variables were centered at the mean or, for the effect modification models discussed below, at the tertile cut-point nearest to the mean. Covariate selection for the renal outcome models was previously reported (Weaver et al. 2003).

Finally, models with cross-product terms of the lead measures and age (age was categorized by tertiles) were evaluated, in order to assess effect modification by age on associations between the lead biomarkers and uric acid. In these models, age was also entered into the model as a centered, continuous variable, in order to avoid residual confounding.

Models were evaluated for linear regression assumptions and the presence of outlying points using added variable plots (Weisberg 1985), which are graphical summaries of the relation between Y and a particular X (referred to as X_a below), adjusted for all of the other covariates. Specifically, the residuals of the regression of Y on all of the covariates except X_a are plotted on the Y axis. This is the part of Y not explained by those covariates. Next, the residuals from the regression of X_a on all the other covariates are computed. This is the part of X_a not explained by the other covariates. These residuals are plotted on the X axis. For each plot, two lines were overlaid: the regression line, and a line determined by a scatter plot smoothing method (lowess) that calculates a locally weighted least-squares estimate for each point in the scatter plot (Cleveland 1979). This allows an examination of the data for outliers that are overly influential, as evidenced by inconsistency between the lowess and regression lines (i.e., when one or two data points with both high lead dose and uric acid move the lowess line away from the regression line, they are likely to overly influence the regression line as well). When applicable, models were repeated without outliers. Models were also assessed for collinearity through examination of variance inflation factors and conditional indices.

RESULTS

Selected Demographics, Exposure, and Health Outcome Measures

Information on demographics, lead biomarkers, uric acid levels, renal function, and selected co-morbid conditions is presented in Table 1. Mean (SD) blood, tibia, and DMSA-chelatable lead levels were 32.0 (15.0) μg/dl, 37.2 (40.4) μg/g bone mineral, and 0.768 (0.862) mg/g creatinine, respectively. Values for these lead measures varied over a wide range. Mean values for uric acid and renal outcomes were normal, although the range for each included several abnormal outliers.

Lead Measure Associations With Uric Acid Levels

In linear regression modeling of uric acid levels in all 803 lead workers, after adjustment for age, gender, BMI, and alcohol use, none of the lead measures was associated (Table 2). Next, regression modeling was performed to evaluate whether age, divided into tertiles (≤ 36 years, 36.1 - 46.0 years, > 46.0 years), modified relations between the lead biomarkers and uric acid levels. In models adjusted for age, gender, BMI, and alcohol use, evidence of effect modification by age was observed (Table 3, model 1). Blood and tibia lead, in separate models, were associated with uric acid in participants in the oldest age tertile. As expected, due to the biological inter-relatedness of these variables (discussed in the Methods section and shown in Figures 1 and 2), both lead associations decreased following additional adjustment for systolic blood pressure (Table 3, model 2) and renal function (Table 3, model 3). However, blood lead remained associated with uric acid ($\beta = 0.0156$; $p = 0.01$) when these associations were modeled in the 133 oldest workers who had serum creatinine greater than the median value (0.86 mg/dl).

Associations Between Uric Acid Levels and Renal Outcomes

The six renal function measures were modeled as outcomes to evaluate whether uric acid was associated with renal function in this population of lead workers. Uric acid levels were associated in all renal outcome models except NAG (Table 4). Higher uric acid was associated

with worse renal function as assessed by the clinical measures but, conversely, with lower RBP. These associations remained significant after the lead biomarkers were added into the models.

Effect of Uric Acid Adjustment on Lead Measure Associations in Renal Function Models

Associations between the lead biomarkers and the renal outcomes, after adjustment for uric acid, were modeled in the oldest tertile of workers since the lead biomarkers associations with uric acid were in the oldest subset and associations between higher lead dose and worse renal function were also primarily in this group. The median age of these 266 workers was 51.1 years with a range of 46.0 - 64.8 years. As shown in Table 5, associations between the lead measures and NAG were unchanged after adjustment for uric acid. However, fewer associations between the lead biomarkers and the clinical renal outcomes remained significant ($p \leq 0.05$) after adjustment for uric acid.

DISCUSSION

In this study, we utilized data from the first of three evaluations in a longitudinal study of Korean lead workers to develop hypotheses about causal pathways among lead biomarkers, uric acid, renal function, and blood pressure. First, we evaluated associations of three lead dose biomarkers with uric acid, with and without control for blood pressure and renal function, while controlling for other covariates (Figure 2A). Next, we evaluated associations between uric acid and six renal function outcomes, with and without control for lead, while adjusting for blood pressure and other covariates (Figure 2B). Finally, we examined the effect of uric acid adjustment on associations between the lead biomarkers and renal outcomes, while controlling for other covariates, including blood pressure (Figure 2C).

Blood and tibia lead associations with uric acid were observed in participants in the oldest age tertile, after adjustment for age, gender, BMI, and alcohol ingestion. These associations were diminished after adjustment for blood pressure and renal function, although blood lead remained significantly associated with uric acid in the 133 oldest workers who had serum creatinine greater than the median. Next, uric acid was significantly associated with all renal function outcomes except NAG. Lastly, after adjustment for uric acid, fewer associations between lead biomarkers and the clinical renal outcomes remained significant ($p \leq 0.05$).

It has been recognized for many years that individuals who have been heavily exposed to lead are at increased risk for both gout and renal disease (Shadick et al. 2000; Batuman 1993). In high-level lead exposure, urate clearance is decreased to a greater extent than can be explained by decreased glomerular filtration alone (Emmerson and Ravenscroft 1975). A defect in tubular secretion of urate is thought to be the primary factor involved (Emmerson 1965; Ball and Sorensen 1969; Emmerson and Ravenscroft 1975), although excessive tubular reabsorption (Emmerson et al. 1971) and extra-renal mechanisms such as lead effects on porphyrin metabolism (Emmerson and Ravenscroft 1975) have also been considered. Associations between

lead measures and uric acid have been examined in populations encompassing a wide range of lead doses (Table 6). Relations between lead dose and gout or uric acid have also been studied in various patient populations. Increased EDTA-chelatable lead burdens have been reported in patients who have both gout and renal disease compared to other groups such as patients with gout alone or with renal disease of known non-lead related etiology (Batuman 1993; Sanchez-Fructuoso et al. 1996; Miranda-Carus et al. 1997). Lin and co-workers (2001) measured blood lead and EDTA-chelatable lead in 67 patients with chronic renal insufficiency and gout and 34 patients with chronic renal insufficiency only. Mean blood lead levels were similar in the two groups (5.4 and 4.4 μg/dl, respectively), but mean EDTA-chelatable lead levels (138.1 and 64.2 μg/72 hours, respectively) were significantly ($p < 0.01$) different. All four uric acid measures were associated EDTA-chelatable lead after adjustment for age, sex, BMI, daily protein intake, and creatinine clearance. Next, 30 participants with chronic renal insufficiency, gout, and EDTA-chelatable lead levels between 80.2 and 361 μg/72 hours were randomized to either a treatment group receiving 1 gram EDTA per week for 4 weeks (N = 20) or to a control group who received glucose in normal saline infusions. The two groups had similar uric acid, renal function, and lead measures pre-chelation. In the treated group, mean EDTA-chelatable lead declined from 159.2 to 41 μg/72 hours; mean serum urate decreased from 10.2 to 8.6 mg/dl ($p = 0.02$ for % change, compared to the control group), and mean urate clearance increased from 2.7 to 4.2 ml/min ($p < 0.01$ for % change, compared to the control group). Mean creatinine clearance also increased from 50.8 to 54.2 ml/min ($p = 0.06$ for % change, compared to the control group). Similar uric acid findings, including results from chelation, were noted in a population of 111 participants with normal renal function, of whom 27 had gout (Lin et al. 2002).

The data discussed above and presented in Table 6 are generally consistent with the premise that in young, otherwise healthy workers, a higher lead dose, such as mean blood lead level > 50-60 μg/dl (or perhaps higher, since neither Wang et al. [2002] nor Ehrlich et al. [1998]

adjusted for blood pressure or renal function), is required before associations with uric acid are present. However, in studies that include participants with other risk factors for elevated uric acid, such as older age or co-morbid conditions, lower lead levels are associated with increases in uric acid.

High levels of uric acid are known to be nephrotoxic; however, controversy exists as to whether observed relations between lower levels of uric acid and renal dysfunction are causal or due to confounding. Johnson and colleagues recently developed a rodent model of hyperuricemia. As noted in the Introduction, a range of adverse renal and vascular outcomes, similar to those noted in humans with primary hypertension (Mazzali et al. 2002) and/or renal dysfunction (Nakagawa et al. 2003) was observed in these rats. In humans, uric acid was found to be associated with reduced renal blood flow and increased renal vascular resistance in patients with primary hypertension (Messerli et al. 1980). Thus, uric acid may be nephrotoxic at lower levels than previously recognized, as opposed to being simply a marker for other renal risk factors.

Many mechanisms for the adverse affect of lead on the kidneys, either directly or through the vascular system, have been proposed (Vaziri 2002; Nolan and Shaikh 1992; Sanchez-Fructuoso et al. 2002). One mechanism not commonly considered in low to moderate lead exposure is via increased uric acid. However, there are a number of similarities between the renal and vascular effects reported in Johnson and colleagues' low level uric acid model and the effects from lead exposure. Tubulointerstitial fibrosis, a classic (although non-specific) finding in lead exposure, was observed in the uric acid model in the absence of the urate crystals that are commonly seen in this pathology at higher levels of hyperuricemia (Mazzali et al. 2001a). Glomerular hypertrophy was reported in hyperuricemic rodents (Nakagawa et al. 2003); Inglis et al. (1978) reported this in adults who survived childhood lead poisoning. Afferent renal arterial thickening was also observed in hyperuricemic rats (Mazzali et al. 2002). Renal vascular disease

in lead-exposed humans has been reported in several case series (Inglis et al. 1978; Morgan et al. 1966; Wedeen et al. 1975). Sanchez-Fructuoso and co-workers (2002) recently reported hypertrophy of the medium and small renal arteries and arterioles in rats whose blood lead levels ranged from 52.9 μg/dl to 33.2 μg/dl at day 90 (when lead ingestion ceased). However, these vascular abnormalities were not observed in rats whose lead exposures, over a 12 month period, were either lower (blood lead levels ~ 20 to 30 μg/dl) (Khalil-Manesh et al. 1993) or much higher (blood lead levels 45.5 to 125.4 μg/dl, averaged over a 12 month period) (Khalil-Manesh et al. 1992) Uric acid was not measured in these rodent studies, however, Goyer (1971) reported hyperuricemia that was not thought to be related to extent of renal insufficiency in lead-exposed rats which suggests that lead may be one of the exposures that does increase uric acid in rats despite the presence of the uricase enzyme. Mazzali and colleagues (2001a) reported that increased systolic blood pressure was correlated with serum uric acid. Increased systolic blood pressure was associated with lead dose in the same Korean lead worker population studied in this report (Lee B-K et al. 2001); similar associations have also been reported in other populations (Sharp et al. 1987). Increased juxtaglomerular renin staining was present in the uric acid model (Mazzali et al. 2001a). Data suggest that lead exposure also increases renin; this effect may vary with length of exposure. Several reviews have concluded that renin is increased with short to moderate term lead exposure in both animals and humans, but is normal or decreased with prolonged exposure (Vander 1988; Gonick and Behari 2002; Sharp et al. 1987). Decreased neuronal nitric oxide (NO) synthase expression in the macula densa was reported in rodents in the uric acid model (Mazzali et al. 2001a). In contrast, the effect of lead on NO does not involve decreased NO synthase expression (Vaziri 2002). In fact, just the opposite occurs, since lead exposure generates oxidants that deplete NO, and NO synthase expression is up-regulated in response.

In conclusion, our data suggest that, at the moderate levels of lead exposure present in

our population, older workers comprise a susceptible population for increased uric acid. This is consistent with the published literature, as noted above. The impact of adjustment for renal function and blood pressure suggests that the effect of lead on uric acid may be mediated through these pathways (Figure 2A). However, since blood lead remained associated with uric acid in our most susceptible group (the oldest workers who had the greatest renal dysfunction), even after adjustment for renal function and blood pressure, mechanisms other than decreased glomerular filtration, such as decreased tubular secretion or even extra-renal mechanisms, may be involved at these exposure levels. Since our data (and those of others [Shadick et al. 2000]) suggest an effect of lead on uric acid beyond that due to renal dysfunction alone, and since uric acid was associated with adverse renal outcomes and resulted in reduced significance of lead biomarker associations in our population, uric acid may be one mechanism through which lead is nephrotoxic. However, this is not the only mechanism for lead-related nephrotoxicity. In our data, the association between blood lead and serum creatinine remained significant ($p < 0.05$) even after adjustment for uric acid. Associations between lead dose and NAG were unchanged and uric acid was inversely associated with RBP. The effects of lead and uric acid on the NO system are also different. Thus, other mechanisms must be involved.

Conclusions regarding causality in this study must be limited since it is cross-sectional. An additional limitation is that we were not able to adjust for the use of medications that influence uric acid since Koreans are not routinely provided with the names of their medications. However, few participants reported any prescription medication use. Our results do suggest that further evaluation of relations among the lead dose biomarkers, uric acid, and renal function in our longitudinal dataset would be of value. This is particularly true since these mechanistic relations may be clinically important. EDTA chelation has been reported to improve both renal function and urate clearance in patients with renal insufficiency and gout, even when EDTA-chelatable lead body burdens were quite low (Lin et al. 2001). If this work is replicated in other

populations and low level uric acid is nephrotoxic, uric acid should also be monitored in patients who are in the early stages of diseases, such as early chronic renal insufficiency, and whose lead body burdens are amenable to chelation.

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Figure legends.

Figure 1. Biological relations among lead, uric acid, blood pressure, and renal function variables.

[a] uric acid is an established nephrotoxicant at high levels; the threshold for renal toxicity is uncertain

[b] the association between uric acid levels and increased blood pressure may be causal or due to confounding. Specifically, high uric acid levels may cause hypertension secondary to renal dysfunction but whether low level uric acid causes primary hypertension is less certain.

Figure 2. Biological relations among variables in models from Tables 3-5. Figure 2A shows associations of lead biomarkers with uric acid (dark arrow) in Model 1, Table 3. The striped arrows represent the blood pressure pathway added in Model 2, Table 3. Checkerboard arrows represent the renal function pathway added in Model 3, Table 3. Figure 2B shows relations between uric acid levels and renal function outcomes. Data in Table 4 control for blood pressure (striped arrows). Lead biomarkers (checkerboard arrow) were also added to these models (Table 5 shows selected models in the oldest tertile of workers). Figure 2C depicts associations of lead biomarkers, uric acid and blood pressure with renal function outcomes (presented in Table 5). These models specifically assessed the effect of uric acid (checkerboard arrows) on the main association between lead biomarkers and renal outcomes (dark arrow), while controlling for blood pressure (striped arrows) and other covariates.

Table 1. Selected Demographic, Exposure and Health Outcome Measures of 803 Current and Former Lead Workers, South Korea

Characteristic	Number	%
Gender		
Male	639	79.6
Female	164	20.4
Work status		
Current lead worker	709	88.3
Former lead worker	94	11.7
Diabetes	6	0.8
Hypertension	58	7.2
Regular analgesic use	16	2.0
Alcohol use		
Never	233	29.1
Current use	521	65.0
Past use	48	6.0
Tobacco use		
Never	255	31.8
Current use	458	57.1
Past use	89	11.1

	Mean	SD	Range
Age, years	40.4	10.1	17.8 - 64.8
BMI, kg/m^2	23.0	3.0	15.7- 34.2
Systolic blood pressure, mm Hg	123.2	16.3	83.7- 215.3
Diastolic blood pressure, mm Hg	75.7	12.0	36.0 - 126.7
Blood lead, μg/dl	32.0	15.0	4.3 - 85.7
Tibia lead, μg Pb/g bone mineral	37.2	40.4	-7.4 - 337.6
DMSA-chelatable lead, mg Pb/g creatinine[a]	0.768	0.862	0.02 - 8.98
Lead job duration, years	8.2	6.5	<1 - 36.2
Uric acid, mg/dl	4.8	1.2	1.4 - 12.3
BUN, mg/dl	14.4	3.7	6 - 32.2
Serum creatinine, mg/dl	0.90	0.16	0.48 - 2.5
Measured creatinine clearance, ml/min[a]	114.7	33.6	11.8 - 338.9
Calculated creatinine clearance, ml/min	94.7	20.7	41.1- 184.5
NAG, μmol/h/g creatinine	215.3	188.5	13.8 - 2577.0
RBP, μg/g creatinine	63.6	190.6	5.2 - 4658.7

[a] n = 787

Table 2. Linear regression models to evaluate associations of lead dose biomarkers with uric acid levels (N = 803)[a]

Model	Lead Variable	β coefficient	SE β	p-value	Model r^2
1	Tibia lead, μg Pb/g bone mineral	-0.0005	0.0010	0.62	0.32
2	Blood lead, μg/dl	0.0027	0.0027	0.32	0.31
3	DMSA-chelatable lead, μg Pb/g creatinine	0.0259	0.0431	0.55	0.31

[a]Uric acid was modeled separately as the outcome, with one of the three lead biomarkers included per model. Regression results from each model are presented only for the association of the lead biomarker with uric acid. Models were also adjusted for age, gender, BMI, and alcohol use.

Table 3. Linear regression models to evaluate effect modification by age in tertiles on associations of blood and tibia lead with uric acid in all lead workers with outliers removed (model 1), with additional control for systolic blood pressure (model 2) and serum creatinine (model 3) (N = 803)[a]

	Model 1			Model 2			Model 3		
Variable	β coeff	SE β	p-value	β coeff	SE β	p-value	β coeff	SE β	p-value
Intercept	4.9217	0.0757	< 0.01	4.9350	0.0759	< 0.01	4.8528	0.0736	< 0.01
Age, years	-0.0182	0.0039	< 0.01	-0.0199	0.0040	< 0.01	-0.0210	0.0039	< 0.01
Systolic blood pressure, mm Hg	----	---	---	0.0047	0.0023	0.04	0.0046	0.0022	0.04
Serum creatinine, mg/dl	----	---	---	----	---	---	2.1830	0.2666	< 0.01
Blood lead, μg/dl	0.0111	0.0041	< 0.01	0.0105	0.0041	0.01	0.0071	0.0039	0.07
Blood lead x agecat2	-0.0109	0.0057	0.05	-0.0107	0.0056	0.06	-0.0063	0.0054	0.25
Blood lead x agecat1	-0.0150	0.0058	0.01	-0.0148	0.0058	0.01	-0.0107	0.0056	0.06
Intercept	4.8932	0.0749	< 0.01	4.9087	0.0750	< 0.01	4.8430	0.0735	< 0.01
Age, years	-0.0155	0.0039	< 0.01	-0.0174	0.0040	< 0.01	-0.0184	0.0038	< 0.01
Systolic blood pressure, mm Hg	----	---	---	0.0052	0.0022	0.02	0.0048	0.0022	0.03
Serum creatinine, mg/dl	----	---	---	----	---	---	2.1808	0.3189	< 0.01
Tibia lead, μg Pb/g bone mineral	0.0036	0.0018	0.04	0.0031	0.0018	0.08	0.0019	0.0017	0.28
Tibia lead x agecat2	-0.0057	0.0028	0.04	-0.0053	0.0028	0.06	-0.0019	0.0028	0.49
Tibia lead x agecat1	-0.0071	0.0029	0.02	-0.0067	0.0029	0.02	-0.0044	0.0029	0.13

[a] Models were also adjusted for gender, BMI, and alcohol use. The oldest age tertile is the reference category. Slopes in the middle (agecat2) and youngest (agecat1) age categories are obtained by adding their respective beta coefficients (of the cross-product term for age x lead) to the beta coefficient of the reference category (oldest age group). P-values for the cross-product terms reflect the statistical significance of the difference between the slopes of the regression line in that age category and the regression line for the oldest age group.

Table 4. Linear regression models to evaluate associations of uric acid with renal outcomes while controlling for covariates (N = 803) [a]

Model	Renal Function Outcome	Uric acid β coefficient	SE β	p-value
1	BUN, mg/dl	0.4186	0.1246	< 0.01
2	Serum creatinine, mg/dl	0.0267	0.0038	< 0.01
3	Measured creatinine clearance, ml/min	-2.5300	0.9791	0.01
4	Calculated creatinine clearance, ml/min	-2.1700	0.4662	< 0.01
5	ln NAG, ln (μmol/h/g creatinine)	-0.0262	0.0210	0.21
6	ln RBP, ln (μg/g creatinine)	-0.1067	0.0254	< 0.01

[a] each renal outcome was modeled separately. Regression results from each model are presented only for the association of uric acid with the renal outcome. BUN, serum creatinine, measured creatinine clearance, and calculated creatinine clearance models were adjusted for age, gender, BMI, current/former worker status and hypertension. NAG and RBP models were adjusted for age, gender, BMI, systolic blood pressure, current/former worker status, alcohol ingestion, and diabetes.

Table 5. Linear regression models to evaluate associations of lead dose biomarkers and uric acid levels with renal outcomes in 266 lead workers in the oldest tertile of age[a]

Renal Outcome	Model 1 (lead biomarker)			Model 2 (uric acid)			Model 3 (combined)		
Independent Variables	β coeff	SE β	p-value	β coeff	SE β	p-value	β coeff	SE β	p-value
BUN (mg/dl) models									
Blood lead, μg/dl	0.0352	0.0183	0.05	-------	------	------	0.0293	0.0185	0.11
Uric acid, mg/dl	-------	------	------	0.4663	0.2307	0.04	0.3963	0.2343	0.09
Serum creatinine (mg/dl) models									
Blood lead, μg/dl	0.0016	0.0006	< 0.01	-------	------	------	0.0012	0.0006	0.03
Uric acid, mg/dl	-------	------	------	0.0245	0.0072	< 0.01	0.0215	0.0073	< 0.01
Tibia lead, μg Pb/g bone mineral	0.0004	0.0002	0.03	-------	------	------	0.0003	0.0002	0.06
Uric acid, mg/dl	-------	------	------	0.0246	0.0072	< 0.01	0.0233	0.0072	< 0.01
Measured creatinine clearance (ml/min) models									
Blood lead, μg/dl	0.1187	0.1177	0.31	-------	------	------	0.1697	0.1198	0.16
Uric acid, mg/dl	-------	------	------	-2.4871	1.4456	0.09	-2.9352	1.4769	0.05
Calculated creatinine clearance (ml/min) models									
Blood lead, μg/dl	-0.1221	0.0594	0.04	-------	------	------	-0.0950	0.0600	0.11
Uric acid, mg/dl	-------	------	------	-2.0384	0.7487	< 0.01	-1.8095	0.7604	0.02
ln NAG (ln [μmol/h/g creatinine]) models									
Blood lead, μg/dl	0.0089	0.0028	< 0.01	-------	------	------	0.0092	0.0028	< 0.01
Uric acid, mg/dl	-------	------	------	-0.0115	0.0364	0.76	-0.0289	0.0361	0.42

Tibia lead, µg Pb/g bone mineral	0.0023	0.0008	< 0.01	-------	------	------	0.0023	0.0008	< 0.01
Uric acid, mg/dl	-------	------	------	-0.0070	0.0366	0.85	-0.0094	0.036	0.80
DMSA-chelatable lead, mg Pb/g creatinine	0.1931	0.0511	< 0.01	-------	------	------	0.1944	0.0512	< 0.01
Uric acid, mg/dl	-------	-----	------	-0.0182	0.0373	0.63	-0.0235	0.0363	0.52

[a] BUN, serum creatinine, measured creatinine clearance, and calculated creatinine clearance models were also adjusted for age, gender, BMI, current/former worker status, and hypertension. NAG and RBP models were adjusted for age, gender, BMI, systolic blood pressure, current/former worker status, alcohol ingestion, and diabetes. Only models in which $p \leq 0.05$ for the lead variable without uric acid adjustment are shown, with the exception of the measured creatinine clearance model; this model is included because the p-value for the beta coefficient of the uric acid variable decreased to ≤ 0.05 after adjustment for blood lead.

Table 6. Summary of selected publications[a] that have evaluated lead measure associations with uric acid.

Study	N	Mean Age	Mean Blood or Bone Lead[b]	Association	P-value of lead measure	Co-variates controlled for	Comments
Wang et al. (2002)	229	65% <40	67.7 µg/dl in males 48.6 µg/dl in females	10 µg/dl increase in blood lead associated with a 0.085 mg/dl increase in uric acid	0.02	gender and body weight	alcohol apparently not significant
Ehrlich et al. (1998)	382	41	53.5 µg/dl 69.7 µg/g	current and historical blood lead in quintiles associated with uric acid	≤ 0.01 for trend	age, height and weight	tibia lead measured on a random sample of 40 participants
Roels et al. (1994)	76 [c] 68 [d]	44 43	43.0 µg/dl; 66 µg/g 14.1 µg/dl; 21 µg/g	continuous lead measures (workers + controls) with uric acid	NS	not reported	
Baker et al. (1981)	318	36[d] 37[e]	22.4 µg/dl [e] 24.0 µg/dl [f]	continuous blood lead with uric acid	NS	age	
Smith et al. (1995)	691	48	7.8 µg/dl	continuous blood lead with uric acid	NS	age, alcohol, ALAD	
Shadick et al. 2000	777	67	5.9 µg/dl 30.2 µg/g patella lead 20.8 µg/g tibia lead	blood lead and uric acid patella lead and uric acid tibia lead and uric acid	0.1 0.02 0.06	age, BMI, diastolic blood pressure, alcohol, serum creatinine	Normative Aging Study

[a] based on sample size and extent of statistical analysis
[b] µg/g indicates µg/g tibia lead per bone mineral unless noted as patella
[c] lead workers
[d] controls
[e] rural residence
[f] urban residence

Figure 1

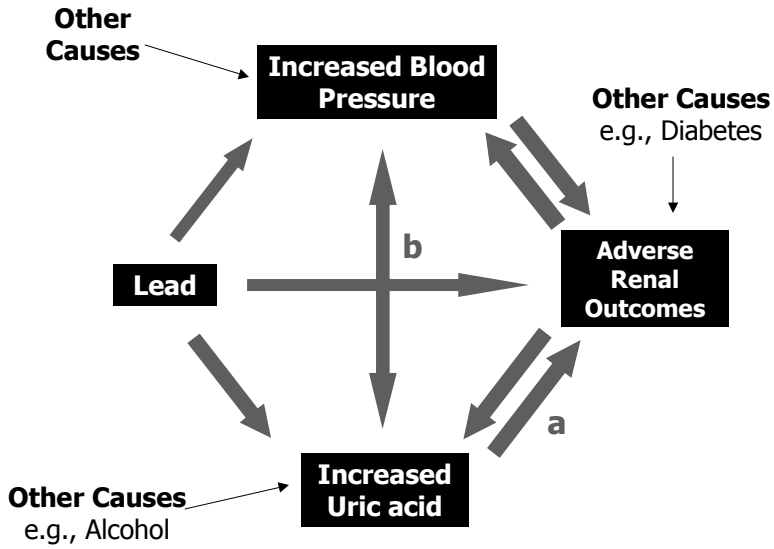
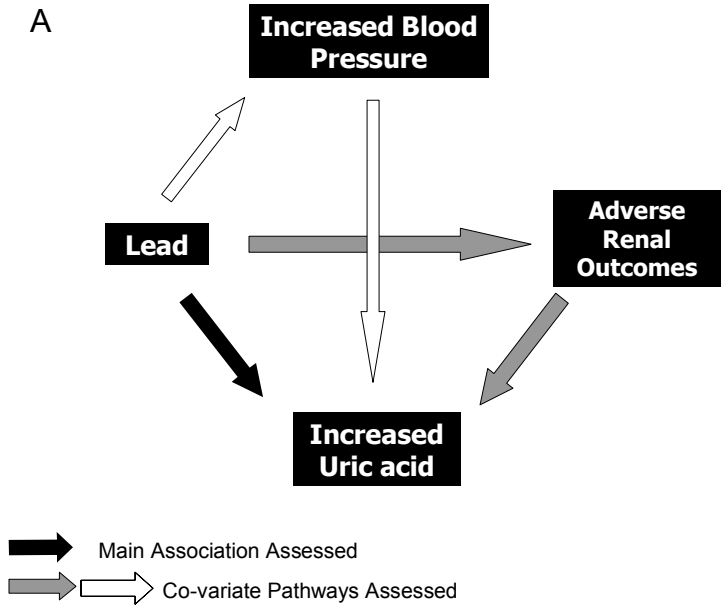


Figure 2



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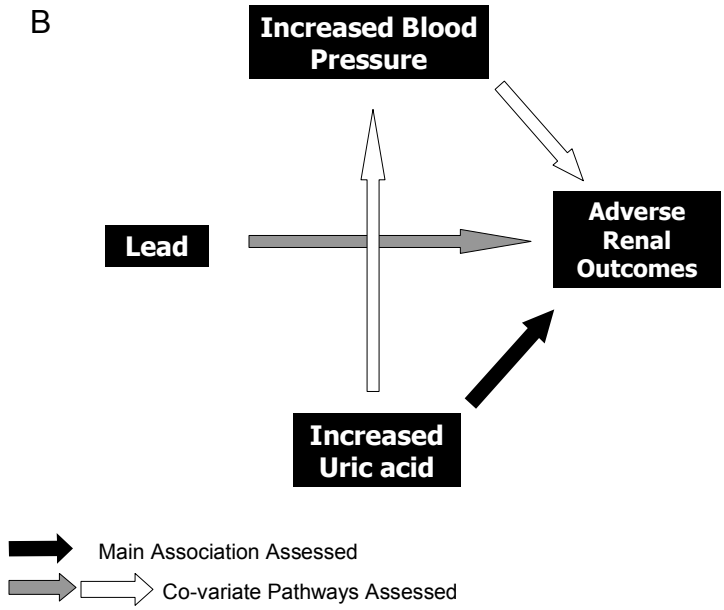
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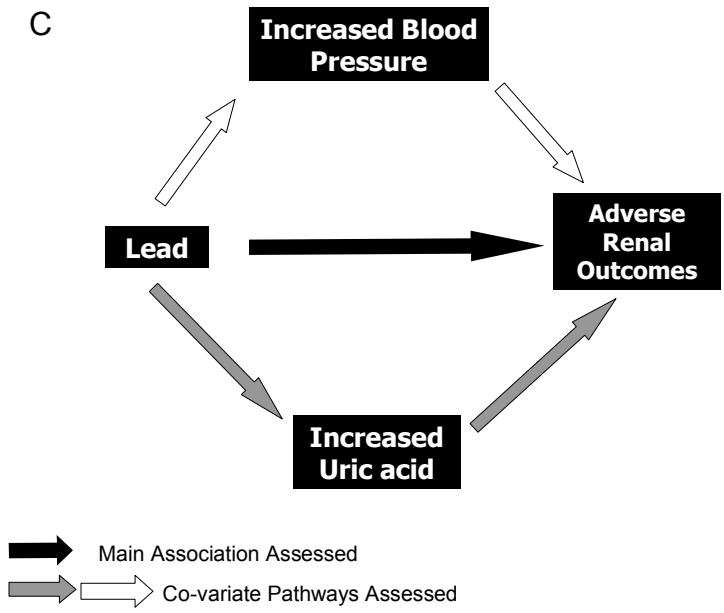
Lead
Adverse Renal Outcomes
Increased Uric acid
Main Association Assessed
Co-variate Pathways Assessed

C


Increased Blood Pressure
Lead
Adverse Renal Outcomes
Increased Uric acid
Main Association Assessed
Co-variate Pathways Assessed